(FILE 'MEDLINE' ENTERED AT 09:25:23 ON 27 MAR 2003)

L1	1434	SEA FILE=MEDLINE	ABB=ON	PLU=ON	"ANGIOGENESIS INHIBITORS "/CT
L2	52396	SEA FILE=MEDLINE	ABB=ON	PLU=ON	COLLAGEN/CT
L3	159	SEA FILE=MEDLINE	ABB=ON	PLU=ON	L1 AND L2
L4	59297	SEA FILE=MEDLINE	ABB=ON	PLU=ON	ANTIBODIES/CT
L5	3	SEA FILE=MEDLINE	ABB=ON	PLU=ON	L3 AND L4

- Key terms

L1	1434	SEA FILE=MEDLINE	ABB=ON	PLU=ON	"ANGIOGENESIS INHIBITORS "/CT
L2	52396	SEA FILE=MEDLINE	ABB=ON	PLU=ON	COLLAGEN/CT
L3	159	SEA FILE=MEDLINE	ABB=ON	PLU=ON	L1 AND L2
L6	70825	SEA FILE=MEDLINE	ABB=ON	PLU=ON	PEPTIDES/CT
L7	6502	SEA FILE=MEDLINE	ABB=ON	PLU=ON	"PEPTIDES, CYCLIC"/CT
L8	9026	SEA FILE=MEDLINE	ABB=ON	PLU=ON	OLIGONUCLEOTIDES/CT
L9	116468	SEA FILE=MEDLINE	ABB=ON	PLU=ON	PROTEINS/CT
L10	6	SEA FILE=MEDLINE	ABB=ON	PLU=ON	L3 AND (L6 OR L7 OR L8 OR L9)

L11 6 L10 NOT L5

L11 ANSWER 1 OF 6 MEDLINE
AN 2002619760 MEDLINE
TI Inhibition of retinal neovascularization by intraocular viral-mediated delivery of anti-angiogenic agents.
AU Auricchio Alberto; Behling Kathryn C; Maguire Albert M; O'Connor Erin M; Bennett Jean; Wilson James M; Tolentino Michael J
SO MOLECULAR THERAPY, (2002 Oct) 6 (4) 490-4.
Journal code: 100890581. ISSN: 1525-0016.
AB Neovascularization characterizes diabetic retinopathy and choroidal neovascularization associated with age-related macular degeneration, the most common causes of severe visual loss in the developed world. Gene transfer to the eye using adeno-associated viral (AAV) vectors is a promising new treatment for inherited and acquired ocular diseases. We used an AAV vector with rapid onset and high levels of gene expression in the retina to deliver three anti-angiogenic factors (pigment epithelium-derived factor, tissue inhibitor of metalloproteinase-3, and endostatin) to the eyes of mice in a mouse model of retinopathy of prematurity. All three vectors inhibited ischemia-induced neovascularization.

L11 ANSWER 2 OF 6 MEDLINE
AN 2002324596 MEDLINE
TI Angiostatic proteins and peptides.
AU Bouma-ter Steege J C; Mayo K H; Griffioen A W
SO CRITICAL REVIEWS IN EUKARYOTIC GENE EXPRESSION, (2001) 11 (4) 319-34. Ref: 130
Journal code: 9007261. ISSN: 1045-4403.
AB Angiogenesis, or the formation of new vasculature out of preexisting capillaries, is a sequence of events that is essential in the normal physiological processes of tissue growth and in a broad spectrum of pathologies. The diseases in which angiogenesis plays a key role are divided into diseases that are characterized by hypoxia/ ischemia and diseases that are dependent on neovascularization. The formerpathologies may benefit from therapeutic angiogenesis

stimulation. This review concentrates on the different strategies to inhibit angiogenesis in diseases that are characterized by excessive angiogenesis, for example, cancer, arthritis, diabetic retinopathy, and inflammatory diseases. These diseases are dependent on the development of newvasculature, and hence, a large variety of different strategies to inhibit angiogenesis are underwayin laboratories throughout the world. At present, over250 angiogenesis inhibitors are described, and approximately half of them display activity in in vivo models. A large percentage of these molecules are natural, nonnatural, or synthetic so-called small molecules. Others are of protein origin, either endogenous or exogenous by nature. The authors highlight the current knowledge on the development of angiostatic proteins and peptides and their potential in the treatment of disease.

L11 ANSWER 3 OF 6 MEDLINE
AN 2002049445 MEDLINE
TI Cloning and antitumor activity of angiogenesis inhibitor HIAF-1.
AU Guo W; Yang Z; Liu J
SO CHUNG-HUA CHUNG LIU TSA CHIH [CHINESE JOURNAL OF ONCOLOGY], (2000 Jan) 22 (1) 19-21.
Journal code: 7910681. ISSN: 0253-3766.
AB OBJECTIVE: A new angiogenesis inhibitor HIAF-1 (human inhibitor angiogenesis factor-1) was cloned, expressed in E. coli and its antitumor activity was studied. METHODS: HIAF-1 was amplified by RT-PCR from human fetal liver tissue, then cloned into pET30a(+) vector and expressed in E. coli BL21:DE3 after sequencing. In vitro endothelial proliferation inhibiting activity of HIAF-1 was examined by MTT method. In vivo antitumor activity was studied in a murine model of IVTA2MA-891. RESULTS: HIAF-1 was first cloned from human fetal liver tissue. Sequence analysis of the inhibitor revealed identity to a c-terminal fragment of human collagen XVIII. HIAF-1 was effectively expressed in E. coli with a yield of 88 mg/L. Recombinant HIAF-1 protein could inhibit endothelial cell proliferation in vitro with an IC50 value of 7.5 micrograms/ml. In vivo studies showed that HIAF-1 inhibited growth rate of the primary tumor by 46.6% and metastasis by 68.9%. CONCLUSION: The cloned and the bio-engineering product of HIAF-1 is an angiogenesis inhibitor, capable of inhibiting tumor growth and metastasis.

L11 ANSWER 4 OF 6 MEDLINE
AN 2001367966 MEDLINE
TI Anti-angiogenic treatment strategies for malignant brain tumors.
AU Kirsch M; Schackert G; Black P M
SO JOURNAL OF NEURO-ONCOLOGY, (2000 Oct-Nov) 50 (1-2) 149-63. Ref: 156
Journal code: 8309335. ISSN: 0167-594X.
AB The use of angiogenesis inhibitors may offer novel strategies in brain tumor therapy. In contrast to traditional cancer treatments that attack tumor cells directly, angiogenesis inhibitors target at the formation of tumor-feeding blood vessels that provide continuous supply of nutrients and oxygen. With respect to brain tumor therapy, inhibitors of angiogenesis display unique features that are unknown to conventional chemotherapeutic agents. The most important features are independence of the blood-brain barrier, cell type specificity, and reduced resistance. Malignant brain tumors, especially malignant gliomas, are among the most vascularized tumors known. Despite multimodal therapeutic approaches, the prognosis remains dismal. Thus, angiogenesis inhibitors may be highly effective drugs against

these tumors. In a clinical setting, they could be applied in the treatment of multiple tumors or postsurgically as an adjuvant therapy to prevent recurrence. This article provides an overview of current anti-angiogenic treatment strategies with emphasis on substances already in clinical trials or candidate substances for clinical trials. The cellular and molecular basis of these substances is reviewed.

L11 ANSWER 5 OF 6 MEDLINE
AN 2001111810 MEDLINE
TI The angiogenesis inhibitor endostatin impairs blood vessel maturation during wound healing.
AU Bloch W; Huggel K; Sasaki T; Grose R; Bugnon P; Addicks K; Timpl R; Werner S
SO FASEB JOURNAL, (2000 Dec) 14 (15) 2373-6.
Journal code: 8804484. ISSN: 0892-6638.
AB Endostatin is a cleavage product of collagen XVIII that strongly inhibits tumor angiogenesis. To determine if endostatin affects other angiogenic processes, we generated full-thickness excisional wounds on the back of mice that were systemically treated with recombinant murine endostatin. No macroscopic abnormalities of the wound healing process were observed. Histological analysis revealed normal wound contraction and re-epithelialization, but a slight reduction in granulation tissue formation and reduced matrix deposition at the wound edge. The blood vessel density in the wounds of endostatin-treated mice was not affected. However, ultrastructural analysis demonstrated severe abnormalities in blood vessel maturation. The wound vessels in the endostatin-treated mice were narrowed or closed with an irregular luminal surface, resulting in a severe reduction in the number of functional vessels and extravasation of erythrocytes. Endostatin treatment did not affect the expression level and localization of collagen XVIII mRNA and protein. Furthermore, the angiogenesis regulators vascular endothelial growth factor, angiopoietin-1, and angiopoietin-2 were normally expressed in the wounds of endostatin-treated mice. However, expression of the major wound matrix proteins fibronectin and collagens I and III was significantly reduced. This reduction is likely to explain the reduced density of the wound matrix. Our results demonstrate that endostatin treatment reduces the number of functional blood vessels and the matrix density in the granulation tissue, but does not significantly affect the overall wound healing process.

L11 ANSWER 6 OF 6 MEDLINE
AN 2000207100 MEDLINE
TI Wielding more power over angiogenesis.
AU Habeck M
SO MOLECULAR MEDICINE TODAY, (2000 Apr) 6 (4) 138-9.
Journal code: 9508560. ISSN: 1357-4310.

FILE 'HCAPLUS' ENTERED AT 09:29:58 ON 27 MAR 2003
L12 3 S HUI77 OR HUI 77
L13 2 S L12 AND ANGIOGENESIS(S)INHIBIT?

L13 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:839607 HCAPLUS
TITLE: Ionizing radiation modulates the exposure of the HUIV26 cryptic epitope within collagen type IV

during angiogenesis

AUTHOR(S): Brooks, Peter C.; Roth, Jennifer M.; Lymberis, Stella C.; DeWyngaert, Keith; Broek, Daniel; Formenti, Silvia C.

CORPORATE SOURCE: Department of Radiation Oncology, New York University School of Medicine, New York, NY, USA

SOURCE: International Journal of Radiation Oncology, Biology, Physics (2002), 54(4), 1194-1201
CODEN: IOBPD3; ISSN: 0360-3016

PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Purpose: The majority of the research on the biol. effects of ionizing radiation has focused on the impact of radiation on cells in terms of gene expression, DNA damage, and cytotoxicity. In comparison, little information is available concerning the direct effects of radiation on the extracellular microenvironment, specifically the extracellular matrix and its main component, collagen. We have developed a series of monoclonal antibodies that bind to cryptic epitopes of collagen Type IV that are differentially exposed during matrix remodeling and are key mediators of angiogenesis. We have hypothesized that ionizing radiation might affect the process of angiogenesis through a direct effect on the extracellular matrix and specifically on collagen Type IV. Methods and Materials: Angiogenesis was induced in a chick chorioallantoic membrane (CAM) model; 24 h later, a single-dose treatment with ionizing radiation (0.5, 5, and 20 cGy) was administered. **Angiogenesis** was assessed, and the exposure of two cryptic regulatory epitopes within collagen Type IV (**HUI77** and HUIV26) was studied in vitro by solid-phase ELISA and in vivo by immunofluorescence staining. Results: A dose-dependent redn. of **angiogenesis** with max. **inhibition** (85%-90%) occurring at 20 cGy was demonstrated in the CAM model. Exposure of the cryptic HUIV26 site, an **angiogenesis** control element, was **inhibited** both in vitro and in vivo by the same radiation dose, whereas little if any change was obsd. for the **HUI77** cryptic epitope. Conclusions: A dose-dependent alteration of the functional exposure of the HUIV26 cryptic epitope is induced by radiation in vitro and in the CAM model in vivo. This radiation-induced change in protein structure and function may contribute to the inhibitory effects of ionizing radiation on new blood vessel growth and warrants further studies in other models.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:475678 HCAPLUS

DOCUMENT NUMBER: 133:99569

TITLE: Method and composition for **angiogenesis inhibition** and detection using antagonists binding to proteolyzed or denatured collagen

INVENTOR(S): Brooks, Peter; Petitclerc, Eric; Xu, Jingsong

PATENT ASSIGNEE(S): University of Southern California, USA

SOURCE: PCT Int. Appl., 92 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000040597	A1	20000713	WO 2000-US383	20000106
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2358517	AA	20000713	CA 2000-2358517	20000106
EP 1149111	A1	20011031	EP 2000-904246	20000106
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002539076	T2	20021119	JP 2000-592305	20000106

PRIORITY APPLN. INFO.:

US 1999-114877P	P	19990106
US 1999-114878P	P	19990106
US 1999-143534P	P	19990713
US 1999-152496P	P	19990902
WO 2000-US383	W	20000106

AB The invention describes methods for **inhibiting angiogenesis** in a tissue by administering an antagonist that specifically binds to a proteolyzed or denatured collagen but not to native triple helical forms of the collagen. Antagonists of the invention can target e.g. denatured collagens type I, type II, type III, type IV, type V, and combinations thereof. Methods using such antagonists for therapeutic treatment of tumor growth, tumor metastasis or of restenosis also are described, as are methods to use such antagonists as diagnostic markers of angiogenesis in normal or diseased tissues both in vivo and ex vivo. Antagonists include monoclonal antibodies referred to as **HUI77**, HUIV26, and XL313.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO, CANCERLIT' ENTERED AT 09:31:24 ON 27 MAR 2003)
L14 5 S L13
L15 2 DUP REM L14 (3 DUPLICATES REMOVED)

L15 ANSWER 1 OF 2 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2002659886 MEDLINE
DOCUMENT NUMBER: 22307236 PubMed ID: 12419448
TITLE: Ionizing radiation modulates the exposure of the HUIV26 cryptic epitope within collagen type IV during angiogenesis.
AUTHOR: Brooks Peter C; Roth Jennifer M; Lymberis Stella C; DeWyngaert Keith; Broek Daniel; Formenti Silvia C
CORPORATE SOURCE: DepartmentS of Radiation Oncology and Cell Biology, The Kaplan Cancer Center, New York University School of Medicine, Rusk Building Room 806, 400 East 34th

Street, New York, NY 10016, USA..
peter.brooks@med.nyu.edu
CONTRACT NUMBER: CA 50263 (NCI)
CA 74132 (NCI)
CA 91645-01 (NCI)
SOURCE: INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY, BIOLOGY, PHYSICS, (2002 Nov 15) 54 (4) 1194-201.
Journal code: 7603616. ISSN: 0360-3016.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 20021107
Last Updated on STN: 20021217
Entered Medline: 20021210

AB PURPOSE: The majority of the research on the biologic effects of ionizing radiation has focused on the impact of radiation on cells in terms of gene expression, DNA damage, and cytotoxicity. In comparison, little information is available concerning the direct effects of radiation on the extracellular microenvironment, specifically the extracellular matrix and its main component, collagen. We have developed a series of monoclonal antibodies that bind to cryptic epitopes of collagen Type IV that are differentially exposed during matrix remodeling and are key mediators of **angiogenesis**. We have hypothesized that ionizing radiation might affect the process of **angiogenesis** through a direct effect on the extracellular matrix and specifically on collagen Type IV. METHODS AND MATERIALS: **Angiogenesis** was induced in a chick chorioallantoic membrane (CAM) model; 24 h later, a single-dose treatment with ionizing radiation (0.5, 5, and 20 cGy) was administered. **Angiogenesis** was assessed, and the exposure of two cryptic regulatory epitopes within collagen Type IV (**HUI77** and HUIV26) was studied in vitro by solid-phase ELISA and in vivo by immunofluorescence staining. RESULTS: A dose-dependent reduction of **angiogenesis** with maximum **inhibition** (85%-90%) occurring at 20 cGy was demonstrated in the CAM model. Exposure of the cryptic HUIV26 site, an **angiogenesis** control element, was **inhibited** both in vitro and in vivo by the same radiation dose, whereas little if any change was observed for the **HUI77** cryptic epitope. CONCLUSIONS: A dose-dependent alteration of the functional exposure of the HUIV26 cryptic epitope is induced by radiation in vitro and in the CAM model in vivo. This radiation-induced change in protein structure and function may contribute to the **inhibitory** effects of ionizing radiation on new blood vessel growth and warrants further studies in other models.

L15 ANSWER 2 OF 2 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002223899 EMBASE
TITLE: Strategies for vascular targeting in tumors.
AUTHOR: Brekken R.A.; Li C.; Kumar S.
CORPORATE SOURCE: S. Kumar, Department of Pathology, University of Manchester, Stopford Building, Oxford Road, Manchester M13 9PT, United Kingdom.
MDDPSSK2@FS1.SCG.MAN.AC.UK
SOURCE: International Journal of Cancer, (10 Jul 2002) 100/2 (123-130).

Refs: 107
ISSN: 0020-7136 CODEN: IJCNAW
COUNTRY: United States
DOCUMENT TYPE: Journal; (Short Survey)
FILE SEGMENT: 016 Cancer
037 Drug Literature Index
LANGUAGE: English

FILE 'HOME' ENTERED AT 09:32:13 ON 27 MAR 2003